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United States Patent [19][11] **Patent Number:** **5,116,978****Mathiapararam**[45] **Date of Patent:** **May 26, 1992**

- [54] **PROCESS FOR BIS(INDOLYL)ETHYLENE SYNTHESIS**
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 [73] **Assignee:** Appleton Papers Inc., Appleton, Wis.
 [21] **Appl. No.:** 615,731
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Related U.S. Application Data

- [63] Continuation-in-part of Ser. No. 320,642, Mar. 8, 1989, Pat. No. 4,996,328.
 [51] **Int. Cl.⁵** C07D 413/00
 [52] **U.S. Cl.** 544/144; 544/142; 544/143; 546/200; 546/201; 548/452; 548/454; 548/455
 [58] **Field of Search** 548/455, 454, 452; 544/142, 143, 144; 546/200, 201

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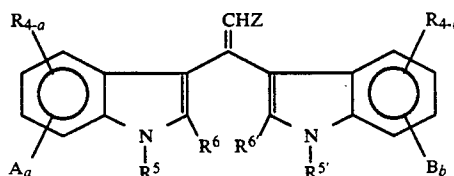
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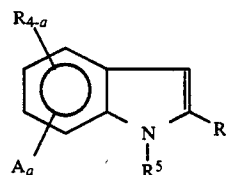
Primary Examiner—Marianne Cintins
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ABSTRACT

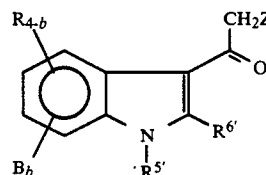
A process for producing a bis-(indolyl)ethylene of the formula



is described, wherein A, B, a, b, R, Z, R⁵, R⁶ and R^{6'} are as defined in the specification, said method comprising reacting an indole of the formula



with an acylindole of the formula



in the presence of a Vilsmeier reagent selected from the group consisting of phosphoryl chloride, phosgene, oxalyl chloride, benzoyl chloride, thionyl chloride, alkanesulfonyl chloride, arene-sulfonyl chloride, alkylchloroformate, and arylchloroformate, together with a Lewis Acid selected from the group consisting of zinc chloride, boron trifluoride and aluminum chloride.

6 Claims, 2 Drawing Sheets

Fig. 1a

Scheme A

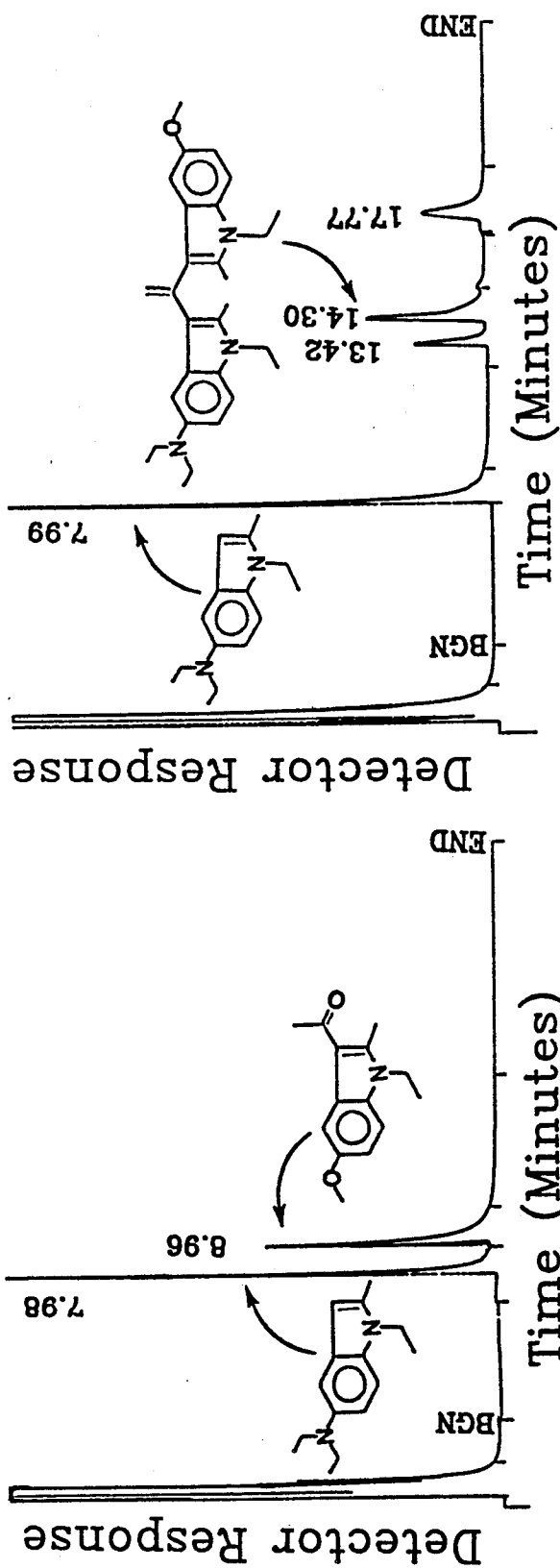
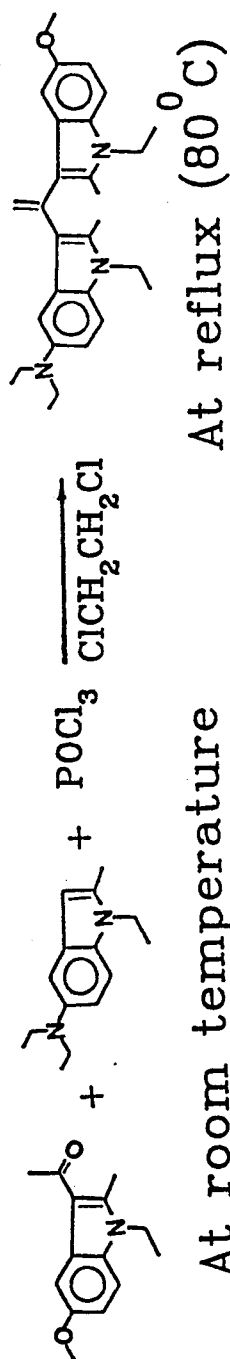


Fig. 1c

Fig. 2a
Scheme B

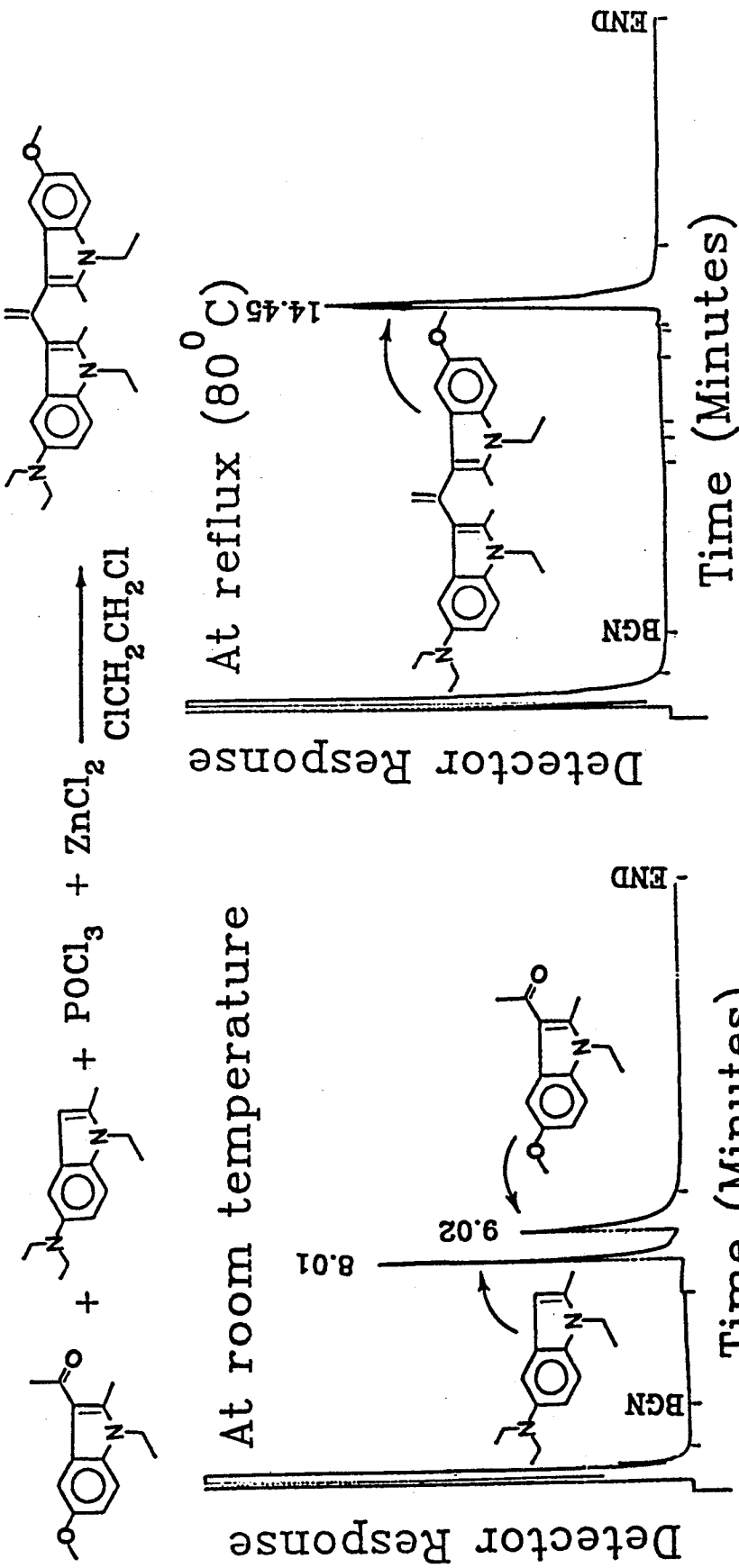


Fig. 2c

U.S. Pat. Nos. 4,897,494 and 4,931,567 disclose several symmetrical bis-(indolyl)ethylene compounds. Unsymmetrical types of bis-(indolyl)ethylenes are not taught or suggested.

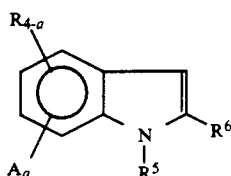
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1, comprised of FIGS. 1a, 1b, and 1c, is a gas chromatograph instrument printout of the reaction mixture of an indole with an acylindole in the presence of the Vilsmeier reagent, phosphoryl chloride.

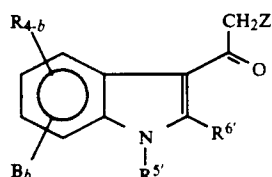
FIG. 2, comprised of FIGS. 2a, 2b, and 2c, is a gas chromatograph printout of the product of reaction mixture of an indole with an acylindole in the presence of the Vilsmeier reagent, phosphoryl chloride and the Lewis Acid, zinc chloride. Note magnitude of bis indolethylene—attributed peak in FIG. 2c as compared to FIG. 1c.

DETAILED DESCRIPTION OF THE INVENTION

This invention teaches an improved process for producing bis(indolyl)ethylenes. The process comprises reacting an indole of the formula

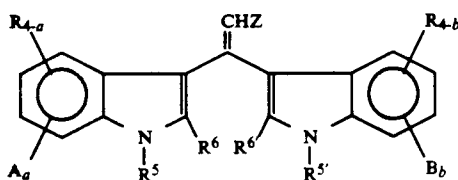


with an acylindole of the formula



in the presence of a Vilsmeier reagent such as phosphoryl chloride, phosgene, oxalyl chloride, benzoyl chloride, thionylchloride, alkanesulfonyl chloride, arenesulfonyl chloride, alkyl chloroformate or aryl chloroformate together with a Lewis acid such as zinc chloride or aluminum chloride. The reaction can be run with or without solvent. Preferred Vilsmeier reagents are phosphoryl chloride, ethyl chloroformate, thionyl chloride, and diethyl chlorophosphate. More preferred is phosphenyl chloride.

In the process of the invention bis-(indolyl)ethylenes of the following formula are prepared:



wherein a is 1 or 2,

wherein b is 1 or 2,

wherein each A is independently selected from a dialkylamino, dialkoxyalkylamino, diaroxyalkylamino, diarylamino, alkylaryl amino, dicycloalkyl-

ylamino, alkylcycloalkylamino, arylcycloalkylamino, pyrrolidino, piperidino, or morpholino radical,

wherein each B is independently selected from A or an alkoxy, alkoxyalkyl or aroxy radical,

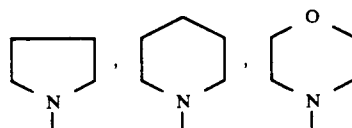
wherein each R is independently selected from hydrogen, halogen, alkyl or alkoxy,

wherein each of R⁵, R^{5'}, R⁶ and R^{6'} are each independently selected from hydrogen, alkyl(C₁-C₈), alkoxyalkyl, aroxyalkyl, cycloalkyl (C₃-C₆), phenyl, and phenyl substituted by alkyl(C₁-C₈) or alkoxy (C₁-C₈),

wherein Z is selected from hydrogen, alkyl(C₁-C₈), alkoxyalkyl, aroxyalkyl, halogen, phenyl or phenyl substituted by alkyl or alkoxy,

the alkyl moieties referred to herein being of one to eight carbons, the cycloalkyl moieties referred to herein being of three to six carbons.

With the pyrrolidino, piperidino or morpholino groups, the following are preferred:



Bonding through sites other than the nitrogen atom can be accomplished for these groups but yields appear reduced.

Vilsmeier reagents include:

(a)	Diethyl Chlorophosphate	(EtO) ₂ POCl
(b)	Phosphoryl Chloride	POCl ₃
(c)	Ethyl Chloroformate	EtOCOC
(d)	Oxalyl Chloride	(COCl) ₂
(e)	Thionyl Chloride	SOCl ₂
(f)	Phosgene Iminium Chloride	[Cl ₂ C=N(CH ₃) ₂] ⁺ Cl ⁻
(g)	Phenyl Dichlorophosphate	PhOPOCl ₂

(a) to (c) of the Vilsmeier reagents are preferred. (d) to (g) find use with aroxy bearing reactants, but are typically too active for alkoxy bearing reactants.

Lewis Acids are substances that coordinate with an electron pair to form a complex. Lewis Acids include ZnCl₂, BF₃ preferably as the etherate, AlCl₃ and the like. ZnCl₂ is preferred herein.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular embodiments disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes can be made by those skilled in the art without departing from the spirit and scope of the invention. Unless otherwise indicated, all measurements are on the basis of weight and in the metric system.

EXAMPLE 1

Condensation of 5-diethylamino-1-ethyl-2-methylindole with 3-acetyl-1-ethyl-5-methoxy-2-methylindole using Phosphoryl chloride

[Scheme A, FIG. 1]

5-Diethylamino-1-ethyl-2-methylindole(1.2 g, 5 mmoles), 3-acetyl-1-ethyl-5-methoxy-2-methylin-

dole(1.4 g, 6 mmoles) and Phosphoryl chloride(0.8 g, 5.2 mmoles) in 1,2-dichloroethane(20 ml) was stirred at room temperature in a flask equipped with a magnetic stirrer and a reflux condenser carrying a drying tube. After two hours, the gas chromatographic analysis of the reaction mixture indicated no reaction, only the starting materials were present. Then, the reaction mixture the reaction mixture was refluxed overnight and monitored by gas chromatography. The reaction mixture contained a mixture of products: 5-diethylamino-1-ethyl-2-methylindole(one of the starting materials), 1-(5-diethylamino-1-ethyl-2-methylindole-3-yl)-1-(1-ethyl-5-methoxy-2-methylindole-3-yl)ethylene (expected product) and two other unidentified products.

EXAMPLE 2

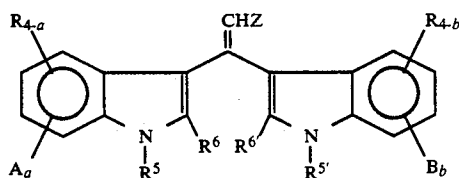
Condensation of 5-diethylamino-1-ethyl-2-methylindole with 3-acetyl-1-ethyl-5-methoxy-2-methylindole using Phosphoryl chloride and zinc chloride

[Scheme B, FIG. 2]

5-Diethylamino-1-ethyl-2-methylindole(230 mg, 1 mmole),3-acetyl-1-ethyl-5-methoxy-2-methylindole(250 mg, 1.08 mmoles), Phosphoryl chloride(170 mg, 1.1 mmoles) and zinc chloride(150 mg, 1.1 mmoles) in 1,2-dichloroethane(5 ml) was stirred at room temperature in a flask equipped with a magnetic stirrer and a reflux condenser carrying a drying tube. After two hours, gas chromatographic analysis of the reaction mixture indicated no reaction. Then, the reaction mixture was refluxed overnight and monitored by gas chromatography. The reaction mixture contained 1-(5-diethylamino-1-ethyl-2-methylindole-3-yl)-1-(1-ethyl-5-methoxy-2-methylindole-3-yl)ethylene as the major product.

What is claimed is:

1. A process for producing a bis-(indolyl)ethylene of the formula



wherein a is 1 or 2,

wherein b is 1 or 2,

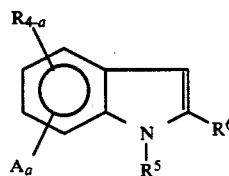
wherein each A is selected from the group consisting of a dialkylamino, dialkoxyalkylamino, diaroxylalkylamino, diarylamino, alkylarylamine, dicycloalkylamine, alkylcycloalkylamine, arylcycloalkylamine, pyrrolidino, piperidino, and morpholino radical,

wherein each B is selected from the group consisting of A, alkoxy, alkoxyalkyl and aroxy radical, wherein each R is selected from the group consisting of hydrogen, halogen, alkyl, and alkoxy,

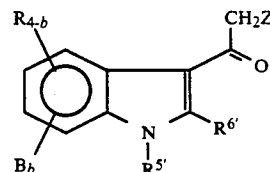
wherein each of R⁵, R^{5'}, R⁶, and R^{6'} are selected from the group consisting of hydrogen, alkyl (C₁-C₈), alkoxyalkyl, aroxyalkyl, cycloalkyl (C₃-C₆), phenyl, and phenyl substituted by alkyl (C₁-C₈) or alkoxy (C₁-C₈),

wherein Z is selected from the group consisting of hydrogen, alkyl (C₁-C₈), alkoxyalkyl, aroxyalkyl, halogen, phenyl, and phenyl substituted by alkyl or alkoxy,

the alkyl moieties referred to herein being of one to eight carbons, the cycloalkyl moieties referred to herein being of three to six carbons, said method comprises reacting an indole of the formula



with an acylindole of the formula



in the presence of a Vilsmeier reagent selected from the group consisting of phosphoryl chloride, phosgene, oxalyl chloride, benzoyl chloride, thionyl chloride, alkanesulfonyl chloride, arenesulfonyl chloride, alkylchloroformate, and arylchloroformate, together with a Lewis Acid selected from the group consisting of zinc chloride, boron trifluoride, and aluminum chloride.

2. The process according to claim 1 wherein the Vilsmeier reagent is phosphoryl chloride.

3. The process according to claim 1 wherein the Vilsmeier reagent is diethyl chlorophosphate.

4. The process according to claim 1 wherein the Vilsmeier reagent is ethyl chloroformate.

5. The process according to claim 1 wherein the reaction of indole with acylindole is carried out in an organic solvent.

6. The process according to claim 5 wherein the solvent is dichloroethane.

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